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Clinical characteristics and prognosis of patients with adult T-cell leukemia-lymphoma

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Abstract

Introduction: The objective of this study was to determine the clinical characteristics and prognosis of patients with adult T-cell leukemia/lymphoma (ATL) at the National Institute of Neoplastic Diseases (INEN) of Peru.

Methodology: A cross-sectional study was carried out, 188 clinical histories and pathological studies of patients diagnosed with HTLV-1 infection diagnosed at the INEN for ten years, of whom 150 had ATL, were reviewed.

Results: Sixty-two percent of the patients had the ATL lymphoma subtype, 37% had the acute subtype, and 1% had the chronic subtype. The median age was 53 (20-89); 51% were women. Within the clinical characteristics: ECOG ≥ 2 (56%); clinical stage III-IV (80%), symptoms B (58%); increased lactic dehydro- genase, LDH, (74%); leukocytosis (50%); hypercalcemia (46%) and anemia (36%). A total of 122 patients (81.3%) received treatment, 79% with chemotherapy (CT) and 4.6% with complementary radiotherapy (RT); CHOP was the most frequent QT regimen (89%). Of the patients with QT, 18% had CR, 32% PR, 7% EE, and 13% PE. The median survival was 3.9 months. In patients who received treatment the median survival was 5 and in those who did not receive treatment the median survival was 0.6 months.

Conclusion: In this report, in patients with ATL, the lymphoma form was the most frequent subtype, and there was a high prevalence of atypical immunophenotype and poor response to CHOP.

Keywords:
MESH: Adult T-Cell Lymphoma-Leukemia, Human T Lymphotropic Virus Type 1, study characteristics, immunotyping, tertiary treatment.

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a highly aggressive neoplasm that was described as a clinical entity in 1977 in Japan. It presents in adulthood, and its most frequent manifesta- tions are skin lesions, adenopathies, hepatosplenomegaly, and leukocytosis with atypical lym- phoid cells, as well as the presence of markers for T lymphocytes [1, 2].

Gallo et al. in 1980 identified the causative retrovirus, HTLV-1 (Human T Lymphotropic Virus Type I), whose genome was incorporated into the DNA of neoplastic cells from ATL pa- tients [3]. The cumulative incidence of ATL is estimated to be between 2.5% and 5% in HTLV-1 carriers [4, 5].

Initially, described as endemic to the southern islands of Japan, years later, the Caribbean, equatorial Africa, Central, and South America, especially Brazil, were included as areas of high HTLV-1 prevalence [6, 7].

In Peru, the first cases were reported in 1994 by W. Rodríguez et al.; [8] the presence of HTLV-1 was demonstrated in specific populations, and several cases of tropical spastic para- paresis produced by the same agent have been recognized. Its existence was reported in sex workers, pregnant women, and descendants of Japanese immigrants, thus confirming the presence of this retrovirus in our environment and, therefore, the possibility of ATL cases [9- 11].

The diversity of its clinical manifestations and prognosis has led to the classification of ATL into four forms: latent, chronic, lymphoma, and acute, according to the Shimoyama clas-sification [12].

Patients with aggressive forms of ATL (acute and lymphoma) have a poor prognosis due to intrinsic resistance to chemotherapy treatments [12], hypercalcemia [13], and opportunistic infections secondary to the immune deficiency that further complicate treatment [14, 15].

Multiple studies of aggressive forms of ATL have failed to improve survival with poly-chemotherapy with intensified regimens or transplantation [16 - 18], as well as monoclonal antibodies such as anti-CCR4 and anti-CD52, which, although showing antineoplastic activity,have very limited data in clinical trials [19-23].

A significant advance is the use of antiretrovirals in combination with interferon. Bazarbachi et al., in their 2010 meta-analysis, reported an increase in survival at five years for the acute, chronic and latent forms compared to the first line of chemotherapy [23, 24].

This work aims to determine the clinical characteristics, immunophenotype patterns, and response to chemotherapy treatment of patients with ATL in our population, thereby contributing to the knowledge of ATL in Peru and assessing its presence in our environment.

Materials and methods

Study design

The present study is cross-sectional. The source is retrospective.

Study area

The study was carried out at the National Institute of Neoplastic Diseases of Peru statistical service in Lima. The study period was from January 1, 1996, to December 31, 2005.

Universe and shows
The universe was made up of all the patients registered in the institution. The sample size calculation was nonprobabilistic, census type, where all incident cases in the study period were included.

Participants
Cases of patients with a de novo clinical diagnosis of adult T-cell leukemia/lymphoma were included..

Variables
The descriptive variables were age, origin, laboratory tests, flow cytometric immunotyping, treatment, response, and survival.

Procedures, techniques, and instruments.
Data were collected from the institutional clinical history. The diagnosis of ATL was based on histological characteristics, immunohistochemistry, and a positive HTLV-1 serological result by ELISA and integration of the provirus by western blot. Two expert hematopathologists re-viewed the samples.

Clinical and laboratory data from the patient's medical records were analyzed. The immunophenotype results were compiled by markers carried out in a flow cytometry study, which were organized into panels according to what was reported in previous studies.

The evaluation of the forms of ATL was carried out based on the diagnostic criteria of the Shimoyama classification. Treatment efficacy was assessed by overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to death from any cause. PFS was applied for patients with a response to treatment, defined as the time from the start of treatment to the first progression, relapse after response or death from any cause.

Avoidance of bias
To guarantee the reliability of the information, the researchers were trained in data collection and the use of the institutional system. A double checklist was used to include the cases. The data were validated and cured by the principal investigator.

Statistical analysis
Once the information was compiled in an Excel spreadsheet, it was entered into a data matrix of SPSS™ 25.0 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version
25.0. Armonk, NY: IBM Corp.). Descriptive statistics were used based on frequencies and percentages for the qualitative variables and the quantitative measures of central tendency. Survival analysis is reported. Overall survival and progression-free survival were calculated using the Kaplan–Meier method, and the distribution of events was compared using the log-rank test. Comparisons of clinical and prognostic factors were compared using the chi-square or Fisher's exact test and multivariate analysis with the Cox model.

Results

The analysis included 150 patients.

Population characteristics

The data of 150 patients with ATL were analyzed; 103 (68.6%) came from the central coast, and 14 (9.3%) came from the central highlands. The most frequent place of birth was the cen- tral coast in 63 (42%), from the southern sierra in 33 (22%). The departments with the highest incidence were Ancash, Apurímac, Ayacucho, Cuzco, Junín, and Huancavelica. A total of 77 patients (51%) were women, and 73 (49%) were men, whose median age was 53 years with arange of 20 to 89 years (Table 1).

Table 1. Characteristics of the patients.

	No.=150	%
Age:		
Median/range	53/(20 - 89)	
Sex		
Feminine	77	51%
Male	73	49%
ATLL type		
Leukemia shape	55	36.6%
Chronic form	two	1%
Lymphoma Shape	93	62%
Zubrod scale		
0	eleven	7%
1	54	36%
2	53	35%
> 3	31	20.6%
Lymphoma subtype (n:93)	No.	%
clinical stage		
I	two	two%
II	fifteen	16%
II	26	28%
IV.	48	52%
Not evaluable	two	two%
Symptoms		
A	39	42%
B	54	58%
International Prognostic Index		
Low risk	13	14%
Low intermediate	32	3. 4%
High medium	30	32%
High risk	16	17%
Not evaluable	two	two%

Clinical features

The time from the onset of symptoms to diagnosis was 1 to 3 months in 66 cases (44%) and less than one month in 50 (33%). Fifty-eight percent had some B symptoms at diagnosis. Fifty- four patients (36%) presented ECOG 1, 53 patients (35.3%) ECOG 2, and 31 (20.6%) ECOG 3-4.

Regarding ATL subtypes, 93 (62%) had the form of lymphoma, 55 (36.6%) acute, and 2 (1.3%) chronic, and no case of silent form was found (Table 1). In the lymphoma subtype, they pre- sented lymph node localization in 82 cases (88%) and extranodal location in 11 (12%); of the latter, the bone, gastric, and skin presentation stood out. Regarding the clinical stage (CD), 48

patients (52%) presented CD IV, 26 (28%) CD III, 15 (16%) CD II, and 2 (2%) CD I. (Table 1). In the lymphoma form, the international prognostic index (IPI), 13 (14%) were low risk, 32 (34%) had low intermediate IPI, 30 (32%) had high intermediate IPI, and 16 (17%) had high IPI (Table1).

The organs involved at diagnosis were 102 (68%) for lymph node involvement, 44 (29%) for hepatomegaly, 41 (27%) for skin involvement, 35 (23%) for splenomegaly, and 17 (11%) forbone involvement (Table 2).

Table 2. Geographic distribution of patients with ATLL.

	Origin		Birth	
	No.=150	%	No.=150	%
North Coast	6	4	3	two
Central Coast	103	68.6	63	42
South coast	2	1.3	6	4
Sierra Norte	8	5.3	11	7.3
Central Sierra	14	9.3	29	19.3
South Sierra	12	8	33	22
Jungle	5	3.3	4	2.6
Japan	0	0	1	0.7

Table 3. Treatment scheme (OTT).

	Nope	%
Patients without OT	31	
CHOEP	3	3%
CHOEP14	1	1%
CHOP	106	89%
CHOP14	1	1%
CVP	3	2.5%
Others	5	4.2%

C: Cyclophosphamide. H: hydroxydaunorubicin . O: vincristine sulfate (Oncovin). Q: Prednisone. E: Etoposide

Table 4. Response to chemotherapy treatment.

	acute		lymphoma	
	No.=38	%	No.=79	%
Complete answer	3	8%	17	22%
Partial Response	6	16%	32	41%
stable disease	5	13%	2	3%
Disease progression	7	18%	8	10%
Not evaluable	17	4.5%	20	25%

Laboratory pathology features

Regarding laboratory changes at diagnosis, 111 (74%) had increased LDH, 112 (75%) had

thrombocytosis, 75 (50%) had leukocytosis, 69 (46%) had hypercalcemia, and 54 (36%) had some degree of anemia. Fifty-two patients (35%) had elevated creatinine and hypertransami-nasemia, and 64 (43%) and 18 (12%) presented hypoalbuminemia.

Immunophenotypic features

Forty-nine patients underwent immunotyping by flow cytometry; 29 (58.3%) showed the following panel: CD4 (+) CD8 (-) CD25 (+); 5 (10.4%) CD4 (+) CD8 (-); 6 (12%) CD4(+) CD8(-),
CD25(-) and 15 (31.3%) atypical phenotypes such as CD4(+) CD8(+); CD4 (+) CD56(+) CD8(-);CD4(+) CD30(+); CD4(-) CD8(-); CD4(-) CD8(+).

Response to treatment

Of the patients studied, 122 (81.3%) received some treatment; chemotherapy, 119 (79%), and
7 (4.6%) received complementary RT. Eighty-nine (94.6%) received the CHOP regimen, 3 (2.5%)
CVP, and 5 (4.2%) other treatment regimens (Table 3). Twenty-one patients (17.6%) presented
complete response (CR); 38 (32%) presented partial response (PR); 8 (7%) presented stable disease (EE); and 15 (12.6%) presented disease progression (PE). In 37 (31%) patients, the response was not evaluable due to the torpid evolution of the patients. According to the ATL subtype, the acute form had an objective response in 9 (24%), CR in 8%; PR in 16%; EE 5 (13%), and 7 (18%) progressed. For the lymphoma form, the objective response was 49 (63% CR: 22%, PR: 41%), SE 2 (3%), and 8 (10%) progressed. The difference in objective response rates was significant between the lymphoma and acute forms (P<0.001) (Table 4). Of the patients who received chemotherapy, 27 (23%) completed six cycles, 69 (58%) completed fewer than three cycles, and 41 (34%) completed only one cycle; of the latter 39 died from neoplasia and toxicity to treatment. Seventy-six percent of the patients were recidivists, and the most af- fected organs were the skin (38%) and lymph nodes (25%). The most frequent cause of death was complications secondary to neoplasia at 69.4%, followed by primarily opportunistic infections at 27.4%.

Survival

The median PFS was six months, at two years, 6%. When evaluating the lymphoma subtype, it reaches a median of 6.4 months with a rate at two years of 7%. For the acute subtype, this figure decreases to a median of 5.6 months with a rate at two years of 0%, without a significantdifference (P = 0.092) (Table 5).

Overall Survival (OS): In the overall group, the median survival was 3.9 months, with a 2- year rate of 8%. On the other hand, in patients who received treatment, the median survival was five months, with a 2-year rate of 10%; in those who did not receive treatment, the median survival was 0.6 months, with a two-year rate of 0%, with statistical significance (P < 0.001). The median OS in the lymphoma subtype was 7.9 months, with a 2-year rate of 11%, and in the acute form, it was a median of 2.8 months, with a 2-year rate of 4%, with a significant difference (P <0.001). When evaluating OS in patients showing an objective response (CR+PR), a median of 9.4 months was obtained with a 2-year survival of 14%.

In a subanalysis of risk factors (table 6), the presence of B symptoms and leukocytosis was established as a risk factor for reduced survival.

Table 5. Overall survival and progression-free survival.

No.=150	Median	Survival at two years
overall survival	3.9 months	8%
clinical form		
Lymphoma	7.9 months	eleven %
Leukemia	2.8 months	4%
PATIENTS WITH CR+RP	(n=59)	
Overall Survival	9.4 months	14%
Progression Free Survival	6 months	6%
Progression Free Survival Clinical form		
lymphoma	6.4 months	7%
Leukemia	5.6 months	0%

*includes a patient with chronic form.

Table 6. Prognostic factors.

	SG		SLE	
	P	RR	P	RR
Age: >60	0.143	-	0.644	-
Gender: Female	0.966	-	0.511	-
Zubrod : 2-4	0.015	1.77	0.824	-
symptoms: B	0.003	2.12	0.103	-
Clinical form: Leukemia	0.889	-	0.386	-
HB: < 12	0.606	-	0.681	-
Leukocytes: > 10000	0.003	1.93	0.385	-
DHL: >550	0.952	-	0.657	-
hypercalcemia	0.318	-	0.009	2.74

Discussion

The prevalence of ATL increases with age, with the most frequent prevalence ranging from 40 to 70 years, since HTLV-1 has a long incubation period of approximately 30 years, as indicated by a population analysis carried out in Japan, where it was found. An average age of 57 years [12]. Some reviews suggest that in Latin America, the onset of ATL occurs at a younger age. For example, in Colombia, some studies find medians of up to 38 years; in the present study,the median was 53 years [7].

Investigation of HTLV-1 infection in relatives of patients with ATL would be fascinating. The result would clarify whether the transmission is mainly vertical and map endemic and risk areas.

The international prognostic index (IPI) has been reported as an adverse prognostic factor [13, 14, 25-28]; we found in the univariate analysis that prognostic factors for OS at ECOG greater than two and the presence of symptoms B.

ATL was first described by Kiyoshi Takatsuky [1] in 1977 as a clinical entity presenting in adults with frequent skin lesions, adenopathies, hepatosplenomegaly, and leukocytosis with abnormal lymphoid cells, with a T-cell immunophenotype. Shimoyama, in 1991, reported the

diagnostic criteria and types of ATL; the present study provides similar findings, with the most frequently involved organs being the lymph nodes, skin, spleen, and liver. Regarding the types of ATL, a predominance was found for the lymphoma variant, while the percentages initially described by Shimoyama by types of ATL revealed 55% for the acute form, 20% for the lym- phoma form, and 20% for the chronic form.. Beltrán et al. described a percentage of approxi- mately 40% for both the lymphoma form and the acute form. One of the considerations to take into account is that there could be an underreporting of cases since the silent and chronic forms require more specific studies to detect abnormal T lymphocytes, and clinical suspicion is very difficult because they are asymptomatic patients with lymphocytosis or with skin com- promise and are often managed by other specialties. The 2 cases in this study were diagnosedin Japan.

Laboratory alterations are frequently described in ATL, such as increased LDH, hyper- calcemia due to exaggerated activation of osteoclasts, the elevation of beta2 microglobulin, and hypoalbuminemia, among others, which are described as prognostic factors [26-28]. Bel- tran et al. identified elevated levels of B2 microglobulin for the lymphoma type and decreasedalbumin for the acute form as prognostic factors.

Some studies relate hyperleukocytosis as a poor prognostic factor similar to ECOG and DHL; however, there is no consensus on the leukocyte cutoff value [13, 14]. Similarly, in pa- tients with HTLV-1 infection, it has yet to be possible to determine the number of leukocytes to determine the level of risk of developing ATL. Imaizumi [29] described a high risk for those with more than 9000 leukocytes, while Ikeda [30] raised this figure to more than 15,000/dl.

The present study found high percentages of LDH levels, hypercalcemia, and hyperleuko- cytosis, identified in the univariate analysis as adverse prognostic factors for OS leukocytosis greater than 10,000 and for PFS hypercalcemia, similar to those reported in other studies, for which reason efforts should be made to implement a specific prognostic index for ATL that allows us to stratify into risk groups and make better therapeutic decisions.

Another point of interest is that the classic ATL immunophenotype is CD4+ CD8- CD25+; there are isolated reports of cases with aberrant immunophenotypes such as CD4-CD8- ; CD4- CD8+; CD4+ CD8+, among others, which have been related to indolent or aggressive evolution, without attributing a role in the prognosis. Since there are few available studies, more cases are necessary to define the significance of the various immunophenotypes as well as the useof immunophenotypic test standards [28].

In this study, a high percentage (31.3%) of atypical immunophenotypes must be able to correlate well due to the sample size. There are two significant difficulties in treating ATL: 1) the high degree of immunosuppression that leads to the development of severe infections with a high prevalence of opportunistic agents and 2) intrinsic resistance of tumor cells to conventional therapies, which is the first cause of high mortality during treatment. The Japa- nese Clinical Oncology Group (JCOG) [16] evaluated six prospective studies observing poor responses to treatment with conventional CT, with no significant difference between the use or not of anthracyclines or intensification regimens, which would add toxicity without impacton survival.

Other alternatives have also been explored, such as the addition of monoclonal antibodies such as anti-CD52 and anti-CCR4 [22, 23], the use of which is anecdotal. Hence, there is not enough clinical experience to support their use and transplantation [20, 21], and their eligibility

is severely limited by the poor performance status of these patients and severe immunosup-pression.

In the silent forms, such as the latent and chronic forms, antiretroviral therapy could be used, and in selected cases, "watch and wait" [16, 23].

An encouraging advance is using antiretrovirals such as zidovudine (AZT) in combination with interferon. Bazarbachi et al., in their meta-analysis carried out in 2010, reported an in- crease in response rates and survival in the acute, chronic and latent types, while the lym- phoma type would benefit more from chemotherapy treatment, which currently has been added to the treatment regimens used in the institution [27, 30].

These studies have yet to be corroborated by more researchers. In this study, response (CR+RP) was achieved in 49.6% of patients, with a high recurrence rate (76%) and nondurableresponses, confirming the aggressive nature of this disease.

Complications secondary to neoplasia were the leading cause of death, followed by in-fections.

OS and PFS are low for this type of lymphoma, whose characteristics are aggressiveness and poor response to different treatments. Various studies confirm these data; the largest was that of Shimoyama in 1991 [12], which indicates figures of 6.2 months for the acute phase,
10.2 months for the lymphoma phase, and 24.3 for the chronic phase. Survival at two years is 16%, 21%, and 52.4%. This study corroborates the significance of each subtype and the treat-ment, which only delays the outcome of this disease.

It should be noted that of the patients who achieved complete remission, one was chronic.

It is noteworthy that two cases of the lymphoma form survived for more than one year and only presented LDH alterations and skin involvement, which reminds us of the fifth form of ATL described by Bittencourt [15] in patients with Bahía-Brasil, which only has skin commit- ment. These patients influenced the progression-free survival curve, which showed a trend but no significant difference for this ATL subtype (P =0.092). Investigation of HTLV-1 infection in relatives of patients with ATL would be of special interest, the result of which would allow us to clarify whether the transmission is mostly vertical and to map endemic and risk areas.

Conclusions

In the present study, a high incidence of patients from the central-southern highlands of the country was observed; the most common subtype was lymphoma, with a high prevalence of atypical immunophenotype in this population, poor response to chemotherapy treatment, and short survival. We identified ECOG greater than 2, B symptoms and leukocytosis greater than 10,000, and hypercalcemia for PFS as adverse prognostic factors for OS. These data show that we need to implement better treatment strategies and devise a specific prognostic index for ATL that helps us stratify the treatment type according to the lymphoma subtype.

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Information administrative

Abbreviations

ECOG: Eastern Cooperative Oncology Group, classification.
CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) followed by DHAP (dexamethasone, cytarabine, and cisplatin).
OS: overall survival
PFS: progression-free survival.

Additional Files

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Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Author contributions

Natalia Valdiviezo Lama: 1. Conceptualization, 2. Formal analysis, 3. Research, 4. Methodology, 5. Project administration, 6. Supervision, 7. Validation, 8. Visualization, 9. Writing-original draft, 10. Writing-revision and editing
Carlos Barrionuevo Cornejo: 1. Conceptualization, 2. Formal analysis, 3. Research, 7. Validation, 10. Writing - review and editing.
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Luis Casanova Marquez : 1. Supervision, 7. Validation, 10. Writing-revision and edition:
Claudio Flores Flores: 2. Formal analysis, 3. Research, 4. Methodology, 7. Validation, 8. Visualization, 9. Writing - origi- nal draft.
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Rossana Ruiz Mendoza: 7. Validation, 8. Visualization ,, 10. Writing-revision and editing
Shirley Quintana Truyenque : 1. Conceptualization, 6. Supervision, 7. Validation, 8. Visualization, 10. Writing - revision and editing. All authors read and approved the final version of the manuscript.

Ethics committee approval

It does not apply to observational studies.

Consent for publication

It does not apply when the patients' images, X-rays, or tomographies are not published.

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